

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/DK2005/000062

International filing date (day/month/year)
28.01.2005

Priority date (day/month/year)
30.01.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/11

Applicant
SANTARIS PHARMA AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/DK2005/000062

AP20 Rec'd PCT/PTO 28 JUL 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	6-10
	No: Claims	1-5, 11-29
Inventive step (IS)	Yes: Claims	6, 7
	No: Claims	1-5, 8-29
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

PCT/DK2005/000062

Reference is made to the following documents:

- D1: BRAASCH D.A. et al.: " RNA interference in mammalian cells by chemically-modified RNA " BIOCHEMISTRY, vol. 42, no. 26, 2003, pages 7967-7975;
- D2: WO 03/070918 A (RIBOZYME PHARMACEUTICALS, INCORPORATED (US); McSWIGGEN James; BEIGELMAN Leonid; MACEJAK Dennis; ZINNEN Shawn; PAVCO Pamela; MORRISSEY David; FOSNAUGH Kathy; MOKLER Viktor; JAMISON Sharon) 28 August 2003;
- D3: PARRISH S. et al.: " Functional anatomy of a dsRNA trigger: differential requirement for the two trigger strands in RNA interference " MOLECULAR CELL, vol. 6, November 2000, pages 1077-1087.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- V.1). Document D1 discloses siRNA molecules falling within the terms of claims 1-5, 11-13, 15-25 and 27 (D1: figures 1, 4, 6, 7, and relevant passages throughout the entire document). *Novel*
- V.2). Document D2 discloses siRNA molecules falling within the terms of claims 1-3, 11-15, 20-27, 29 as well as pharmaceutical compositions falling within the terms of claim 28 (D2: pages 133-134, 141-148, and relevant passages throughout the entire

document).

- V.3). The subject-matter of claims **1-5** and **11-29** is therefore not novel (Article 33(2) PCT) because these claims do not contain any feature allowing their subject-matter to be distinguished from the disclosure of documents D1 and D2. Indeed, the term "at least" present in the claims does not exclude that the modified siRNA molecules concerned in the claims have more than one modification in one or both strands.
- V.4). Claims **6-10** formally meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.
- V.5). Claims **6-10** (for claims 8-10, insofar as they depend directly or indirectly on claims 6 and/or 7) meet the requirements of Article 33(3) PCT because no document in the available prior art (see in particular the disclosure of document D3 on page 1084, left column), taken alone or in combination with any other document, suggests that the positions 10 or 11 of the sense strand of a siRNA molecule are particular sensitive to chemical modifications, so that their modification would lead to the effect disclosed in present application.
- V.6). Claims **8-10** (insofar as they depend directly or indirectly on claims 4-7) do not seem to meet the requirements of Article 33(3) PCT because, it should be remarked that the nucleobases mentioned in claims 8-10 are merely obvious possibilities among which the person skilled in the art would choose, without intervention of any inventive skill, in order to provide further chemically modified siRNA molecules.
- In the **absence** of a **functional limitation** of the modified siRNA molecules

concerned in these claims, these modified siRNA molecules should be considered obvious alternatives to the ones disclosed in the available prior art, which would be chosen by the person skilled in the art without intervention of any inventive skill, whenever circumstances require so.

V.7). The industrial applicability of the subject-matter of claims **1-29** is acknowledged (Article 33(4) PCT).

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2004/099387	18 November 2004	6 May 2004	6 May 2003